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OCA PAD AMENDMENT - PROJECT HEADER INFORMATION

08/15/90

Active

Project #: E-19-676 Cost share #:
Center # : 10/24-6-R6745-0A0 Center shr #:
Contract#: GRANT AGMT DTD 5/25/89 Mod #: LTR DTD 6/21/90 Document : GRANT
Prime #:
Contract entity: GTRC

Subprojects ? : N
Main project #:

Project unit: CHEM ENGR Unit code: 02.010.114
Project director(s):
 YOGANATHAN A P CHEM ENGR (404)894-2849

Sponsor/division names: AMERICAN HEART ASSOC /
Sponsor/division codes: 500 / 011

Award period: 890701 to 900630 (performance) 900815 (reports)

Sponsor amount	New this change	Total to date
Contract value	0.00	25,850.00
Funded	0.00	25,850.00
Cost sharing amount		0.00

Does subcontracting plan apply ? : N

Title: VENTRICULAR OUTFLOW OBSTRUCTION IN IHSS: AN IN VITRO STUDY

PROJECT ADMINISTRATION DATA

OCA contact: Kathleen R. Ehlinger 894-4820

Sponsor technical contact

Sponsor issuing office

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ELIZABETH W. NUGENT, M.D., PRESIDENT
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Security class (U,C,S,TS) : U
Defense priority rating : N/A
Equipment title vests with: Sponsor

ONR resident rep. is ACO (Y/N): N
N/A supplemental sheet
GIT X

Administrative comments -

ISSUED TO EXTEND REPORTING DATE FROM 6/30/90 TO 8/15/90.

GEORGE INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 08/23/90

Project No. E-19-676

Center No. 10/24-6-R6745-OA0

Project Director YOGANATHAN A P

School/Lab CHEM ENGR

Sponsor AMERICAN HEART ASSOC/

Contract/Grant No. GRANT AGMT DTD 5/25/89 Contract Entity GTRC

Prime Contract No.

Title VENTRICULAR OUTFLOW OBSTRUCTION IN IHSS: AN IN VITRO STUDY

Effective Completion Date 900630 (Performance) 900815 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	N	
Final Report of Inventions and/or Subcontracts	N	
Government Property Inventory & Related Certificate	N	
Classified Material Certificate	N	
Release and Assignment	N	
Other	N	
Comments		

Subproject Under Main Project No.

Continues Project No.

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Management	Y
Research Security Services	N
Reports Coordinator (OCA)	N
GTRC	Y
Project File	Y
Other	N
	N



E-19-676

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July 29, 1990

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Dr. Randall Tackett
American Heart Association - Georgia Affiliate
Chairman, Research Committee
1685 Terrell Mill Road
P.O. Box 6997
Marietta, GA 30065

Dear Dr. Tackett:

Enclosed are three copies of the terminal report for my research grant titled "Ventricular Outflow Obstruction in IHSS: An In Vitro Study," which was funded during the past fiscal year.

Sincerely,

Ajit P. Yoganathan, Ph.D.
Professor
Co-Director Bioengineering Center

APY/ske

cc:  Ms. K. Ehlinger
Ms. C. Clarkson

July 27, 1990

American Heart Association - Georgia Affiliate
Grant-In-Aid Terminal Report

VENTRICULAR OUTFLOW OBSTRUCTION IN
IHSS: AN IN VITRO STUDY
7/1/89 - 6/30/90.

Professor Ajit P. Yoganathan
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I. PROJECT REPORT

General

A transparent plexiglass model was designed to simulate the left ventricle of the heart. Its shape was based on echocardiographic observations performed at the onset of systole in human patients. Moderate or severe hypertrophy of the septum could also be simulated. An explanted native human valve with an intact papillary muscle apparatus was used in the model. The papillary muscles could be set to nearly any position inside the ventricle. Furthermore, the tension exerted on the two papillary muscles could be adjusted with stepper motors and recorded using load cells. The papillary muscles are attached to metal rods using small polycarbonate disks. The rods are themselves connected to stepper motors that can move a maximum of 600 steps / sec; each step represents 1/1000 inch.

Two flow loops were developed. A steady flow loop was used to simulate a specific period of the cardiac cycle while a pulsatile one simulated the entire cardiac cycle. The pulsatile flow system duplicated the flow curves through the aortic and the mitral valves and the pressure waveforms in the ventricle, the atrium and the aorta. The system also reproduced atrial systole.

These models have been used for two separate projects:

Hypertrophic Cardiomyopathy

Obstructive hypertrophic cardiomyopathy is a common heart disease which is characterized by systolic anterior motion (SAM) of the mitral valve. Until recently, the most common explanation for SAM was the Venturi mechanism which was based on high velocities created by the narrowed outflow tract associated with septal hypertrophy. This Venturi hypothesis, however, failed to explain how SAM can begin when the outflow tract velocities are low or negligible, a common clinical observation. The goal of this study was therefore to investigate a new hypothesis which stresses structural abnormalities of the papillary muscles as a primary cause for SAM.

The beginning of systole, the moment at which SAM starts, was simulated with steady flow experiments using flow rates of up to 30 l/min (corresponding to a cardiac output of 5 l/min). The behavior of the mitral valve in a normal or SAM configuration was also observed throughout the cardiac cycle with the pulsatile flow system, over a cardiac output range of 2 to 8 l/min.

In order to observe the mitral valve configuration and the shape of the ventricular flow field, a 1 mm thick plane of

light was created in the center of the flow chamber, parallel to the long axis of the ventricle. Neutrally buoyant particles were added to the blood analog solution. Their motion closely approximated that of the fluid. As the particles passed through the laser plane, they refracted the light and displayed pathlines. Thus, this flow visualization technique allowed us to obtain two-dimensional qualitative maps of the left ventricular flow field.

In the simulation of a normal heart (papillary muscles in apical, posterior and out position), the mitral valve had a flat anterior leaflet with most of the flow (the outflow tract) passing above it. The streamlines were smooth and followed the shape of the anterior leaflet, going toward the aorta. Then, by displacing the papillary muscles anteriorly and inward, the valve was moved into the outflow tract and SAM was initiated even for low flow rates. When SAM was present, streamlines could be seen impacting the proximal side of the leaflets, causing a drag force which maintained the mitral leaflets in anterior position.

By simulating severe septal hypertrophy, it was possible to achieve velocities as high as 3.5 m/s above the mitral valve. However, as long as the papillary muscles were in normal position (posterior, outward), the mitral valve remained outside of the outflow tract and SAM could not be produced. Displacing the papillary muscles to a more inward and anterior position not only created SAM but also modified dramatically the ventricular flow field. Indeed, the mitral leaflets contacted the hypertrophied septum, obstructing the outflow tract and causing the fluid to recirculate inside the ventricle. In order to exit the ventricle, the flow now had to pass on the sides of the obstruction!

Therefore, these experiments have shown that high velocities above the mitral valve cannot initiate SAM alone, even when the septum is hypertrophied. At the same time, without septal hypertrophy, SAM was initiated even at low flow rates by displacing the papillary muscles to a more anterior (valve moved in the outflow tract) and inward (tension distribution within the leaflets altered and slackness in the center part of the valve, allowing it to move) position. Finally, the combination of papillary muscle displacement and septal geometry modified extensively the ventricular flow field. Thus, it seems that the papillary muscle displacement theory surpasses the Venturi mechanism to describe and explain SAM.

Papillary Muscle Tension

In pulsatile flow, software written in Turbo Pascal was developed for data acquisition in the pulsatile system. With this software, data was acquired in volts from five channels representing two papillary muscle tensions, aortic and mitral flow rates, and ventricular pressure - using an overall

acquisition rate of 500 Hz. The data could be collected with or without the use of papillary muscle tension control. The acquisition of data was initiated using an external trigger from the pulse duplicator box used to produce pulsatile flow. A delay could also be placed between the trigger and the start of the data acquisition to compensate for the time between the electronic trigger and the actual start of mechanical events. After ten cycles were acquired, they were averaged together and the five average wave forms were displayed on the screen. The means and standard deviations per channel over all ten cycles were computed and displayed. The option to acquire ten more cycles was provided. If other cycles were being acquired, the trigger delay could be changed, and the motors could be used to adjust the papillary muscle position. The program could then be reset for controlled or uncontrolled mode. When running the program in the controlled mode, the actual and desired tensions are compared at 10 msec intervals. The desired tension curve is calculated based on the pressure and stroke volume of ten cycles acquired without control. The papillary muscles could be moved a maximum of four steps during one of these intervals. The number of steps to move is calculated from a preset movement sequence combined with proportional integral control using the current error between the desired and actual tensions and the sum of errors. If a trigger delay is entered, instead of waiting to acquire data as in the uncontrolled mode, the desired tension curve and the preset movement sequence are shifted forward. This allows the papillary muscles to be moved during this delay period in order to help build up the tension. After acquiring ten cycles, along with the data displayed in the uncontrolled mode, the error, sum of errors, and motor movement curves are also displayed. The two papillary muscle tension curves are averaged together, filtered and displayed along with the desired tension curve. The motor movement curve can also be stored in a file. An opportunity to adjust the preset movement sequence is also provided at this time.

The effects of left ventricular pressure and cardiac output on papillary muscle tension were investigated independently. The papillary muscles were held stationary in the normal position: low, out, and apical. Two types of mitral annulus rings were used: circular and elliptical. To determine the effect of the left ventricular pressure on papillary muscle tension, the peak ventricular pressure was varied from 80 to 160 mm Hg, at a constant cardiac output. Several cardiac outputs were used ranging from 4 to 8 l/min. Then, to determine the influence of the cardiac output on papillary muscle tension, the cardiac output was varied from 1 to 12 l/min at constant peak ventricular pressures ranging from 90 to 130 mm Hg.

At constant cardiac output, the papillary muscle force increased linearly with the left ventricular pressure ($r=0.99$). Cardiac outputs below 6 l/min had almost no effect on the papillary muscle force. Above 6 l/min, the tension

increased with the square of the flow rate ($r=0.81$), up to 25% compared to low cardiac outputs. These results were observed for both mitral annulus rings.

Moreover, the papillary muscle tension was found to be greater with the elliptical mitral annulus. This result could be explained by Laplace's law stating that the mitral annulus tension equals the radius of curvature of the leaflet multiplied by the pressure gradient across the leaflet.

Consequently, left ventricular pressure as well as cardiac output exert a large influence on the papillary muscle tension. The geometry of the mitral annulus (shape) is also of great importance.

Controlled pulsatile flow experiments were also conducted. The purpose of these experiments was to simulate the physiologic contraction of the papillary muscles by matching the papillary muscle tension to in vivo data published by Salisbury et al. The number of steps to move the motors each period of time (10 msec) was calculated from a preset movement sequence combined with proportional integral control based on the error at that step and the sum of errors. Experiments were performed to determine the best preset movement sequence by setting the control constants to zero. Experiments were also performed to find the best values of the control constants using a preset movement sequence of zero. Finally, the best preset sequence was combined with control.

Results showed that the best matching between the two curves occurred for values of K_p (proportional control constant) and K_i (integral control constant) such that $0.01 < K_p < 0.02$ and $0.001 < K_i < 0.02$. Also, the matching of the two curves depended on the position of the mitral valve. When the valve was in the low, in, apical position, the matching was better than in the normal position case.

Finally, these two separate projects will eventually merge together. The forces exerted on the papillary muscles at the onset of SAM will be calculated using the same load cells. This would provide us more detailed fundamental information concerning the mechanism of this common disease.

Lay Summary

Because of the complex structure of the human mitral valve, it is especially susceptible to disease. A scientific understanding of its intricate workings is not currently available. Therefore, a long term study was undertaken in which an intact mitral valve apparatus could be mounted in a model of the left ventricle for engineering studies. A computer control system was first developed to control muscle movement as it would occur in the human body. After doing this, the patterns of muscle force were studied. Having established physiologic muscle character, the mechanism for systolic anterior motion of the mitral valve in hypertrophic cardiomyopathy was studied. The independent and accurate control of all normal and disease variables in our model allowed two competing hypotheses to be tested. The newest hypothesis, which was confirmed in this study over the existing Venturi theory, may lead to more simple surgical techniques to correct this common problem.

II. COLLABORATORS

- a. Dr. Robert A. Levine was actively involved with the project. He is a co-author on all of the papers and presentations. He visited Georgia Tech three times during the course of the project, and spent 3 to 5 days each time. Furthermore, we had telephone discussions with him concerning the project every week. Dr. Levine also continued parallel work in his animal (model) studies. One of the papers submitted for publication is based on both the in vitro and in vivo studies.
- b. The following graduate students participated in the project:

Elizabeth Giesecking - MS
Edward Cape - PhD Candidate
Xavier Lefebvre - PhD Candidate
Armelle Cagniot - PhD Candidate
Michael Simpson - MS Candidate
Carol Vesier - PhD Candidate

III. PUBLICATIONS

a. Abstracts and Presentations*

- (i) Levine, R.A., Giesecking, E., Lefebvre, X., Cape, E.G., Sung, H-W., and Yoganathan, A.P., "Increased Outflow Tract Velocity Fails to Produce Systolic

* All presentations had abstracts published in the conference proceedings.

Anterior Motion of a Normally Restrained Mitral Valve In Vitro," 62nd Annual Scientific Sessions - American Heart Association, Circulation, 80, pp. II-662, 1989.

- (ii) Levine, R.A., Valahakes, G.J., Lefebvre, X., Giesecking, E., Cape, E.G., Yoganathan, A.P., and Weyman, A.E., "New Insights Into the Mechanisms Obstruction in Hypertrophic Cardiomyopathy: Experimental Models," 62nd Annual Scientific Sessions - American Heart Association, Circulation, 80, pp. II-662, 1989.
- (iii) Vesier, C.C., and Yoganathan, A.P., "A Method for Modeling 3-D Blood Flow in the Left Ventricle," Paper #167Aj, presented at the Annual AIChE Meeting, San Francisco, CA, November 1989.
- (iv) Lefebvre, X. P., Hautanen, K. I., Giesecking, E. R., Cape, E. G., Levine, R. A., and Yoganathan, A. P., "In Vitro Steady and Pulsatile Flow Visualization of the Normal Mitral Valve," Proceedings First International Conference on Visualization in Biomedical Computing, Atlanta, GA, May 1990.
- (v) Lefebvre, X. P., Cagniot, A., Giesecking, E. R., Levine, R. A., and Yoganathan, A. P., "The Mechanism of Systolic Anterior Motion in Obstructive Hypertrophic Cardiomyopathy. In Vitro Steady and Pulsatile Flow Experiments," Proceedings 7th Meeting of the European Society of Biomechanics, pp. 60, Aarhus, Denmark, July 1990.
- (vi) Lefebvre, X. P., Cagniot, A., Giesecking, E. R., Levine, R. A., and Yoganathan, A. P., "Flow Through the Mitral Valve," Proceedings of the 1st World Congress of Biomechanics, San Diego, CA, August 1990.
- (vii) Cape, E. G., Giesecking, E. R., Cagniot, A., Simpson, M. S., Weyman, A. E., Yoganathan, A. P. and Levine, R. A., "A Computer Driven Control System for Sensing and Adjusting Papillary Muscle Tension in an In Vitro Model of Mitral Valve Function," Proceedings Computers in Cardiology Meeting, Chicago, IL, September 1990.
- (viii) Cagniot, A., Lefebvre, X. P., Giesecking, E. R., Yoganathan, A. P. and Levine, R. A., "Ventricular Pressure and Cardiac Output Independently Contribute to Papillary Muscle Tension: A New In Vitro Model of Mitral Restraint." Submitted to 63rd Scientific Sessions of the American Heart Association.

- (ix) Lefebvre, X. P., Cagniot, A., Yoganathan, A. P., Weyman, A. E. and Levine, R. A., "Reproduction of Systolic Anterior Motion of the Mitral Valve in a Pulsatile Flow Model." Submitted to 63rd Scientific Sessions of the American Heart Association.
- (x) Lefebvre, X. P., Giesecking, E. R., Cagniot, A., Levine, R. A. and Yoganathan, A. P., "In Vitro Studies of the Mechanism of Systolic Anterior Motion of the Mitral Valve in Hypertrophic Cardiomyopathy: Steady Flow Studies," Proceedings Biomedical Engineering Society Meeting, Blacksburg, VA, October 1990.

b. Manuscripts

- (i) E. R. Giesecking, E. G. Cape, S. H. Winoto, R. A. Levine, and A. P. Yoganathan, "Microcomputer Based Control on Cardiac Papillary Muscles in an In Vitro Model of the Left Ventricle," Engineering Journal of Singapore, vol. 15, pp. 53-63, 1990.
- (ii) R. A. Levine, G. J. Valahakes, E. R. Giesecking, E. G. Cape, X. P. Lefebvre, A. P. Yoganathan, L. Guerrero, "Insights into the Mechanism of Obstruction in Hypertrophic Cardiomyopathy: Experimental and Clinical Implications," Submitted to Journal of the American College of Cardiology.
- (iii) X. P. Lefebvre, E. R. Giesecking, E. G. Cape, R. A. Levine, and A. P. Yoganathan, "Steady Flow Visualization of the Systolic Anterior Motion of the Mitral Valve in Hypertrophic Cardiomyopathy: An In Vitro Study," Submitted to the Journal of Biomechanical Engineering.
- (iv) X. P. Lefebvre, E. R. Giesecking, E. G. Cape, R. A. Levine, and A. P. Yoganathan, "Pulsatile Flow Visualization of the Systolic Anterior Motion of the Mitral Valve in Hypertrophic Cardiomyopathy: An In Vitro Study," in preparation.

IV. RESEARCH CONTINUATION

- a. This project is being actively continued.
- b. Funding has been obtained from Medtronic, Inc. for \$25,000 per year for two years. We have also received super-computer time from Cray, Inc. valued at about \$250,000 for the next year, to conduct computer simulation studies on the systolic anterior motion of the mitral valve.

A grant to NIH is being planned and is to be submitted in January 1991.